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WASTING SYNDROME AS A RESULT OF THE EXPOSURE OF ALBINO RATS TO 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN (TCDD)

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ABSTRACT :

Polycholorinated dibenzo-*p*-dioxins (PCCDs) are widespread, persistent, and highly toxic environmental pollutants. 2,3,7,8-Tetrachlorodibenzo-*P*-dioxin (TCDD) is the most toxic congener among PCDDs and the most thoroughly investigated model compound of this chemical class. Typical features of TCDD induced lethality are feed refusal, body weight loss, and exhaustion of energy stores, all of which are manifestations of wasting syndrome. The present study was designed to investigate the effects of TCDD on the feed intake, body weight gain, as well as some related parameters including cholesterol, triglycerides, glucose and thyroxin hormone (T4) levels in the serum. Two hundred male albino rats of 10-12 weeks old were divided into five groups (40 in each). The first and second groups were used for acute oral toxicity experiment while the third, fourth and fifth groups were used for long-term experiment. Body weight gain as well as feed intake were recorded weekly.

There was a significant reduction in body weight gain which reached its maximum reduction (17.2%) after 6 weeks in TCDD-treated rats compared to control rats. The average food consumption of TCDD-treated rats was 150g/rat/week while control rats consumed 300g/rat/week. Glucose concentration results recorded a significant decrease in TCDD-treated and Vit. C received groups compared with the control one as this value reached 85.2 mg/dl after 10 weeks of treatment. Cholesterol and triglycerides showed a significant increase after 10 weeks of exposure compared to control, where these values reached 132.34,149.92 mg/dl for cholesterol and 99.64, 96.67 mg/dl for triglycerides in both long term toxicity alone and with Vit. C treatment respectively. Thyroxin hormone values showed a significant decrease than the control also in both groups after 10 weeks of the exposure, where the values were 2.64 and 2.73 mg/dl respectively. TCDD has been shown to have a multitude of effects on intermediary metabolism. Hypoglycemia and hypothyroidism are well documented effects in TCDD-treated rats. These metabolic disorders together with feed refusal, has been suggested to play an important role in TCDD-induced wasting syndrome and lethality in rats.

INTRODUCTION :

Exposure to TCDD may occur through diet especially food from animal origin or from the surrounding environment like soil, water and air as a result of bioaccumulation through food chain (Kreuzer *et al*, 1997). Also occupational exposure through industrial activities was occurred (WHO, 1994). Changes in

carbohydrates and lipid metabolism are very prominent symptoms of high doses of TCDD, resulting mostly in the loss of fat and muscle. The sever form of body-weight loss are described as "Wasting syndrome", the loss of body weight up to 50% is not entirely attributable to the lack of food intake. The explanation of a drastic TCDD-mediated decline in the adipose lipoprotein lipase activity is considered to induce lipolysis in adipose cells and increase in serum lipids as increase cholesterol and triglycerides levels. The wasting syndrome is lethal and develops over a period of a few week (2-3 weeks) in rat. TCDD produced changes in lipid metabolism associated with increase of rat serum cholesterol level (Mitrou *et al*., 2001). Rats administered 2.5, 25, 250 or 1000 ng TCDD/kg b.w/day, showed an increase of cholesterol level (Chu *et al*., 2001). TCDD in a dose of 0.01, 0.1, 1.0 and 3.0µg/kg b.w/day for 91 days revealed an increase in triglycerides levels in all doses in rat (Ivens *et al*.,1993). TCDD administration induced highly increase in lipid concentration in serum including increase of triglycerides levels (Mitrou *et al*., 2001). In monkeys TCDD elevated levels of serum triglycerides (Rier *et al*., 2001). In fact progressive hypoglycemia has been suggested as ultimate cause of TCDD-induced death (Gorski *et al*., 1990). Additional studies have revealed reduced utilization of glucose in Sprague-Dawely rats as early as 1 day after exposure to a lethal dose of TCDD (Weber *et al*., 1987). TCDD administered to male and female rats for 91 days in a dose of 0.01,0.1,1.0 and 3.0 µg/kg b.w by gavage showed a reduction of serum T4 levels in all doses (Ivens *et al*., 1993 and Battershill, 1994). TCDD induced lethality may be due to feed refusal, body weight loss and some other metabolic disorders. The objective of this study was to investigate the relation between TCDD application and the appearance of wasting syndrome. Investigation of the mechanism by which TCDD induces wasting syndrome was also our goal of this study.

MATERIALS AND METHODS:

Chemicals:

TCDD solution (99% purity), was obtained from Grey Hound Company Laboratories, England. It was dissolved in corn oil as vehicle.

Experimental protocol:

200 males albino rats weighting 100-150g of 10-12 weeks old were housed in wire bottom galvanized cages, five rat each. Food and water were provided *ad libitum*. Suitable temperature under 12 h. light/dark cycle was also provided. Forty rats were exposed to oral single dose of 4.4µg/kg b.w diluted in 1ml corn oil, while another forty rats were used as control group for the acute toxicity. Forty rats were exposed to 0.44µg/kg b.w, diluted in 1ml corn oil orally day by day for 12 weeks. Forty rats were exposed to the same previous dose in addition to Vit. C in concentration of 1g/l drinking water simultaneously. Forty rats were administered corn oil only and kept as control for long-term toxicity experiment. Samples were collected at 12, 24, 48, 72, 96 and 144 hours post-exposure in case of acute toxicity, while samples were collected after 4, 6, 8, 10, 12weeks post exposure and after 2, 4 weeks from the stoppage of TCDD exposure in the long term toxicity experiment. Average food consumption as well as body weight gain were recorded weekly. serum glucose concentration and triglycerides were determined colorimetrically according to the method of Trinder (1969). Cholesterol was estimated colorimetrically after the method of Stein (1986). Thyroxin level was determined in serum using enzyme linked immunoassay (ELISA) according to Kaplan (1997). Statistical

analysis of data was conducted using SAS Institute statistical package (1990).

RESULTS:

Body weight gain was severely impaired by 0.44µg/kg of TCDD in the time-course experiment as presented in table (1); Compared to control rats the difference was statistically significant from the second week to the last week after treatment. Rats displayed signs of wasting from the second week of treatment. Reduction of feed intake was also recorded after second week of TCDD treatment and persisted to the end of the experiment as shown in table (1). Rats displayed signs of wasting syndrome from the second week of exposure.

Table (1): Effect of long-term exposure of TCDD and TCDD + Vit. C on body weight and feed intake of albino rats.

Time post exposure (week)	Groups	Body weight (g)	Feed intake (g/rat/day)
1st	TCDD	171± 0.47	24.30 ± 0.22
	TCDD+Vit. C	172 ± 0.79	24.35 ± 0.21
	Control	176 ± 0.89	24.90 ± 0.23
2nd	TCDD	162.12± 0.70 *	18.52 ± 0.21 *
	TCDD+ Vit. C	169.2 ± 0.70 *a	23.65 ± 0.22 *
	Control	184.8 ± 0.63	35.1 ± 0.32
3rd	TCDD	156.82 ± 0.22 *	14.0 ± 0.30 *
	TCDD+ Vit. C	163.17 ±0.34 *a	14.0 ± 0.27 *
	Control	185.15 ± 0.48	34.37 ± 0.34
4th	TCDD	161.58 ± 0.36 *	12.58 ± 0.20 *
	TCDD+ Vit. C	165.8 ± 0.22 *a	15.69 ± 0.89 *
	Control	186.50 ± 0.40	35.89 ± 0.34
5th	TCDD	156.34 ± 0.45 *	13.0 ± 0.26 *
	TCDD+ Vit. C	161.8 ± 0.39 *a	13.14 ± 0.29 *
	Control	181.88 ± 0.29	32.08 ± 0.29
6th	TCDD	149.02 ± 0.55 *	11.25 ± 0.21 *
	TCDD+ Vit. C	152 ± 0.28 *a	12.9 ± 0.19 *
	Control	180 ± 0.41	30.08 ± 0.49
7th	TCDD	154.0 ± 0.65 *	14.46 ± 0.37 *
	TCDD+ Vit. C	162.6 ±0.30 *a	14.56 ± 0.27 *
	Control	183.9 ± 0.59	33.60 ± 1.0
8th	TCDD	167.23 ± 0.59 *	16.13 ± 0.28 *
	TCDD+ Vit. C	172.8 ± 0.65 *a	20.5 ± 0.50 *
	Control	185.6 ± 0.56	35.36 ± 0.56
9th	TCDD	174.8 7± 0.71 *	25.41± 0.59 *
	TCDD+Vit. C	176.41± 0.36 *	26.0± 0.35 *
	Control	199.45 ± 1.4	35.66 ± 0.60
10th	TCDD	188.16± 0.46 *	25.60± 0.58 *
	TCDD+Vit. C	188.08± 0.44 *	25.40± 0.60 *
	Control	216.68 ± 1.3	36.28 ± 0.47
11th	TCDD	203.10 ± 1.3 *	24.0± 0.1 *
	TCDD+Vit. C	215.35± 1.3 *a	23.45± 0.92 *
	Control	281.65 ± 0.92	35.60 ± 0.52
12th	TCDD	222.75± 0.65 *	23.25± 0.62 *
	TCDD+Vit. C	227.25± 0.77 *a	26.30±0.49 *
	Control	250.70±2.023.25	35.10±0.52
13th	TCDD	228.6± 0.56 *	22.9±0.98 *
	TCDD+Vit. C	231.0± 0.64 *a	27.8±0.66 *
	Control	269.9 ± 0.7	33.2± 0.80
14th	TCDD	229.0± 0.39 *	25.50±2.6 *
	TCDD+Vit. C	239.7±0.55 *a	25.20±0.57 *
	Control	270.2 ± 0.98	34.20±1.0
15th	TCDD	246.0± 1.7 *	24.80±1.3 *
	TCDD+Vit. C	251.8± 1.0 *a	26.80±1.3 *
	Control	281.6 ± 1.0	33.60±0.74
16th	TCDD	211.2± 1.8 *	25.60±1.2 *
	TCDD+Vit C	255.40± 0.92 a*	25.80±0.73 *

	Control	290.6 ± 1.2	38.40±0.92

*** Significant at P ≤ 0.05 to 0.01 in comparison with control.**
The letter a indicates significant differences between Vit. C-treated and non treated groups.

Increase in both cholesterol and triglycerides levels in serum leading to hyperlipaemia, while it causes decrease in both glucose and thyroxin (T4) levels in serum leading to hypoglycemia and hypothyroidism as recorded in tables (2 & 3).

Table (2): Acute toxic effect of TCDD exposure on cholesterol, triglycerides, glucose and Thyroxine hormone (T4) levels of albino rats.

Time post Exposure (hours)	Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	Glucose (mg/dl)	Thyroxine hormone (T4) (mg/dl)
12	exposure	76.16 ± 2.09	61.85 ± 0.5	87.64 ± 2.04 *	4.78 ± 0.72
	control	95.33 ± 2.5	60.33 ± 0.57	114.33 ± 2.08	4.76 ± 0.42
24	exposure	114.53 ± 3.36 *	67.14 ± 1.35	93.50 ± 4.2 *	3.77 ± 0.38 *
	control	95.66 ± 3.0	63.65 ± 1.00	117.36 ± 3.5	4.80 ± 0.50
48	exposure	134.01 ± 4.17 *	72.17 ± 2.06 *	91.41 ± 2.61 *	3.0 ± 0.78 *
	control	77.66 ± 5.21	63.34 ± 1.81	111.05 ± 2.89	4.54 ± 0.67
72	exposure	125.16 ± 2.78 *	73.02 ± 1.8 *	85.88 ± 3.60 *	2.95 ± 0.82 *
	control	88.49 ± 2.79	62.64 ± 2.4	120.01 ± 3.96	4.70 ± 0.78
96	exposure	131.201 ± 3.33 *	67.78 ± 2.75 *	103.54 ± 3.33 *	2.81 ± 0.57 *
	control	84.00 ± 3.84	63.90 ± 2.57	109.99 ± 2.73	4.70 ± 0.43
144	exposure	125.46 ± 7.8	63.55 ± 1.6	92.11 ± 1.19 *	3.88 ± 0.74 *
	control	91.00 ± 7.6	62.99 ± 2.8	119.09 ± 5.05	5.51 ± 0.16

*** Significant at P ≤0.05 to 0.01 in comparison with control**

Table (3): Effect of long-term exposure of TCDD and TCDD + Vit. C on cholesterol, triglycerides, glucose and thyroxine hormone (T4) levels of albino rats.

Time post Exposure (week)	Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	Glucose (mg/dl)	Thyroxine hormone (T4) (mg/dl)
4th	TCDD	54.0±1.3	64.74±3.7	83.75±4.8*	2.69±0.27*
	TCDD + Vit. C	67.40±1.6	66.51±3.2	81.81±2.6*	2.65±0.23*
	Control	58.20±1.0	63.25±2.16	109.24±3.0	4.67±0.56
6th	TCDD	79.0±1.6*	75.90±5.4*	63.17±2.15*	2.69±0.69*
	TCDD + Vit. C	92.0±1.3*a	84.11±3.6*	78.87±3.0*a	2.75±0.70*
	Control	59.30±2.0	62.71±2.2	116.0±3.9	4.95±0.65
8th	TCDD	162.6±3.5*	90.99±6.2	91.06±4.0*	2.99±0.42*
	TCDD + Vit. C	205.6±1.8a	89.31±7.9*	48.97±3.2*a	2.99±0.45*
	Control	56.77±2.0*	61.91±1.18	125.98±3.2	4.74±0.93
10th	TCDD	132.34±4.02*	99.64±7.0*	89.2±4.1*	2.64±0.41*
	TCDD + Vit. C	149.92±3.04*a	96.67±5.3*	90.0±1.15*	2.73±0.36*
	Control	56.80±2.5	63.01±1.8	124.32±2.7	4.87±0.61
12th	TCDD	172.32±2.3*	107.35±3.0*	96.34±2.7*	2.83±0.58*
	TCDD + Vit. C	211.0±1.7a	114.64±4.0*a	95.84±2.0*a	2.24±0.87*
	Control	54.80±3.0	63.50±1.49	128.13±3.0	5.04±0.41
14th	TCDD	178.56±4.0*	96.46±2.1*	71.69±1.0*	3.46±0.92*
	TCDD + Vit. C	190.84±2.0*	107.46±3.5a	88.62±3.4*	4.33±0.06a
	Control	52.60±3.0	63.50±1.4	128.13±3.0	5.12±0.66
16th	TCDD	233.8±6.38*	76.41±4.0	74.16±4.50*	3.61±0.968
	TCDD + Vit. C	199.20±4.6*	76.28±2.0	92.19±5.33*a	4.26±0.77a
	Control	52.60±5.0	62.70±2.0	140.42±3.5	5.09±0.44

*** Significant at P ≤0.05 to 0.01 in comparison with control.**
The letter a indicates significant differences between Vit. C- treated and non treated groups.

DISCUSSION:

A significant decrease in both feed intake and body weight gain was recorded in long-term toxicity groups. These results were in agreement with Lutz *et al.* (1994), Lebofsky and Rozman,(1999) and Dunlap *et al.* (1999), they reported that TCDD in very low level doses causes highly decrease in body weight or wasting syndrome. Animal loss about 10% of body weight in one week after TCDD administration, there was a dose dependant decrease in feed consumption and body weight gain indicative to the wasting syndrome (Schiller *et al.*, 2001). Wasting syndrome attributed to TCDD is responsible for the loss of fat and muscle, where TCDD-mediated decline in the adipose lipoprotein lipase activity which induce lipolysis in adipose cells reflected clinically with an increase serum cholesterol and triglycerides levels and decrease serum glucose and thyroxine levels (Hans *et al.*, 1999). Decrease in feed intake was attributed to anorexia which developed as a typical features of TCDD -induced lethality by inducing feed refusal, body weight loss and exhaustion of energy stores (Matti *et al.*, 1995). Restoration of normal value of weight and feed intake did not occur till the end of experimental time in both Vit. C treated and non treated group.

Hyperlipoproteinemia associated with increased level of both cholesterol and triglycerides levels could be attributed to toxic effect of TCDD on lipid metabolism (Mitrou *et al.*, 2001). Lipid metabolism changes presented as an increase in both cholesterol and triglycerides levels can be explained as a result to liver damage and bile duct lesions (Contarow and Trumper, 1962 and Breckinridge *et al.*, 1978). Hyperlipoprotinemia may be also due to changes in thyroid activity, reflected as hypothyroidism (Breckinridge *et al.*, 1978). TCDD has a severe toxic effect on the thyroid gland reflected clinically as decrease in serum thyroxin levels at all dose levels (Ivens *et al.*, 1993 and Battershill, 1994). Restoration of normal values of both cholesterol and triglycerides levels did not occure until the end of the experimental time in all experimental groups except triglycerides level which restored at 144 h of TCDD administration in acute toxicity.

Hyperlipoproteinemia is an obvious syndrome induced by TCDD in different experimental groups. This syndrome developed as a result to direct toxic effect of TCDD on liver, inducing liver damage, obstruction of bile duct and thyroid gland activity, which reflected clinically by changes in lipid metabolism and hypothyroidism. Restoration of normal levels did not occur till the end of the experiment time in all groups indicating no value of Vit. C treatment.

Serum glucose levels showed a significant decrease in all groups. These results were in agreement with Gorski *et al.*(1990) and Weber and Stahl (1994) who reported that Hypoglycemia is a well documented effect in TCDD treated rats. Hypoglycemia was attributed to impaired gluconegenic pathway in combination with reduced feed intake (Matti *et al.*, 1995). Lethal hypoglycemia was due to a reduction in the expression of the key enzyme of gluconegenesis, phosphoenol pyruvate carboxykinase (Seltzer, 1989), and the key enzyme of tryptophan metabolism (Weber and Stahl, 1994). Viluksela *et al.* (1999) added that lethality of TCDD associated with decreased of key gluconegenic enzymes in liver leads to decrease in liver glycogen concentrations. This seems to be secondary to the reduced feed intake.

Restoration of glucose levels to normal values did not occur till the end of experimental time in all experimental groups. Hypoglycemia,

recorded in different experimental groups was due to TCDD toxicity on the liver glycogenesis mechanism, and also to feed refusal. Restoration of normal values did not occur in all experimental groups till the end of the experimental time, indicating no value of Vit. C treatment on this compartment.

The obtained results revealed a significant decrease in thyroxine level in the serum in all experimental groups. The same results were recorded by Weber *et al*. (1992),Weber and Stahl (1994), Lutz *et al*. (1994) and Nishimura *et al*. (1999). They reported that TCDD-induced lethality appeared as a decrease in serum level of thyroxine (T4). Hypothyroidism was contributed to TCDD-effect on the thyroid gland where TCDD treatment in rodents resulting in hypertrophy and hyperplasia of thyroid follicular cells and ultimately leads to thyroid adenoma and carcinoma (Barter and Klaassen, 1992). Hypothyroidism also could be attributed to TCDD-induced T4 glucouronidation by UDP-glucouronosyltransferase-1 and enhanced biliary excretion of glucouronide, which lead to decrease in T4 concentration (Hans *et al*., 1999).

Restoration of normal value of thyroxin did not occur in both acute toxicity and long term groups. While restoration occurred in Vit.C treated group after 2 weeks of TCDD stoppage. As TCDD-induced hypothyroidism in different experimental groups, this toxic effect is variable between the acute and long-term toxicity and with or without Vit. C treatment. This indicates that TCDD toxicity is dose and time dependent. Hypothyroidism was attributed to thyroid gland affection and also due to TCDD-induce T4 glucuronidation which responsible for T4 catabolism or degradation. Restoration of normal values was variable between Vit. C treated and non treated group, which indicate some value of Vit. C in the treatment of the TCDD toxicity. Changes in the carbohydrates and lipid metabolism are very prominent symptoms of high doses of TCDD resulting mostly in the loss of fat and muscles. The sever form of body-weight loss are described as wasting syndrome. TCDD-mediated wasting syndrome through its effect on the lipolysis activity. This syndrome is correlated with increase the cholesterol and triglycerides in the serum. The values of feed intake and body weight gain did not restored till the end of experiment in both Vit. C treated and non treated group indicate that no value of Vit. C treatment on the TCDD toxicity.

REFERENCES:

Barter, R. A., and Klaassen, C. D., (1992): UDP-glucuronyl transferase induces reduce thyroid hormone levels in rats by an extrathyroidal mechanism. Toxicol. Appl. Pharmacol. 133, 36-42.

Battershill, J. M., (1994): Review of the safety assessment of polychlorinated- biphenyl (PCBs) with particular reference to reproductive toxicity. J. Human Exp. Toxicol. Sep; 13 (9): 581-97.

Breckinridge, W. C., Little, J. A., Steiner, G., (1978): Hypertriglyceridemia associated with the deficiency of a lipoprotein. CII. N. Engl. J. Med., 298: 1265-1273.

Chu, I., Lecavalier, P., Hakansson, H., Yagminas, A., Valli, V. E., Poon, P.,and Feeley, A., (2001): Mixture effects of 2,3,7,8-Tetrachlorodibenzo-P-dioxin and polychlorinated biphenyl congeners in rats. J. Chemo-osphere. May-Jun; 43 (4-7): 807-14.

Contarow, A., and Trumper, M., (1962): In clinical Biochemistry, 6 th ed., W. B. Saunders Co. Philadelphia.

Dunlap, D. Y., Moreno, M. J., Nagashima, Z. W., Tessier, M. E., Hansen, and Mastumura, F., (1999): Dioxin, 378, 1034, 1448.

Gorski, J. R., and Rozman, K., (1987): Dose-response and time course of hypothyroidism hypoinsulinema and characterization of insulin hypersensitivity in 2,3,4,8-tetra chlorodibenzo-P-dioxin (TCDD)-treated rats. Toxicology 44, 297-307.

Gorski, J. R., Weber, L. W., D and Rozman, K., (1990): Reduced gluconeogensis in 2,3,4,8-tetra chlorodibenzo-P-dioxin (TCDD)-treated rats. Arch. Toxicol. 64, 66-71.

Hans, M., Siegfried, G., Roger, M., and Frank. W., (1999): Toxicology. 1 st ed. 699-711. Academic Press.

Ivens, I. A., Loser, E., Rinke, M., Schmidt, U.,and Mohr, U., (1993). Subchronic toxicity of 2,3,7,8-Tetrachlorodibenzo-P-dioxin in rats. J. Toxicology, Oct 25; 83 (1-3): 181-201.

Kaplan M. M., (1997): Clinical perspectives in the diagnosis of thyroid disease. Clinical Chemistry. 44: 11; 2143-2148.

Kreuzer, P. E., Csanady, GY. A., Baur, C., Kessler, W., Papke, O., Greim, H., and Filser, J. G., (1997): 2,3,7,8-Tetrachlorodibenzo-P-dioxin(TCDD) and congeners in infants. Arch. Toxicol. 71, 383-400

Lebofsky, M. and Rozman K. K., (1999): Oral toxicity of 1,2,3,4,8-penta chlorodibenzo-P-Dioxin (PCDD) and the rule of inhalation toxicology. Dioxin, 64: 298, 1010-1093.

Lutz W. D. W.; MarhiHa, L; Bernhard, U; S.; Susan S., and Karl, K., R., (1994): Correlation between toxicology and effects on intermediary metabolism in 2,3,4,8-tetrachlorodibenzo-P-dioxin treated male C57BL/6J and DBA/2J mice. Toxicology and Applied Pharmacology, 131; 155-162.

Matti, V., Bernhard, U., Stahl and Karl K. R., (1995): Tissue-Specific effects of TCDD on the activity of phosphoenol pyruvate carboxy kinase (PEPCK) in rats. Toxicol, Appl. Pharmacol. 135, 308-315.

Mitrou, P. I., Dimitriadis G., and Raptis, S. A., (2001): Toxic effects of 2,3,7,8-Tetrachlorodibenzo-P-dioxin and related compounds. Research Institute. Sep: 12 (5): 406-411.

Nishimura, N. Ohsako, S., Ishizuka, M., Tohyama, C., Sone, H. and Yenoemoto, J. (1999):Endocrine function of male rats exposed maternally TCDD. Sot. Annual. Meeting 1014-1034.

Rier, S. E., Coe, C. L., Lemieux, A. M., Martin, DC., Morris, R., Lucier, G. W., Clark, G. G., (2001): Increased tumor necrosis factor-alpha production by peripheral blood leukocytes from TCDD-exposed rhesus monkeys. J. Toxicol. Sci., Apr, 60 (2): 327-37.

SAS Instiute (1990): SAS User's Guide, Version 6.07. SAS Institute, Inc., Cary, North Carolia, USA.

Schiller CM, A. kock CM, Moore RA, and Walden R., (2001): Effect of 2,3,7,8-Tetrachlorodibenzo-P-dioxin (TCDD) and fasting on body weight and lipid parameters in rats. Toxicology. Aug 13; 165 (1): 51-63.

Seltzer, H. S., (1989): Drug-induced hypoglycemia: A review of 1418 cases. Endcrinol. Metab. Clin. North A, 18: 163-183.

Stein EA, (1986): In textbook of Clinical Chemistry, NW Tiez, Ed. W. B. Sounder, Philadelphia. PP. 879-886, 1818, 1829.

Trinder P., (1969): Enzymatic calorimetric test. Clin. Biochem, 6: 24-27

Viluksela, M., Unkil, M., Pohjanvirta, R., Tuomisto, J.T., Slahl, BU., Rozman, R. K.,

Tuomisto, J., (1999): Effects of 2,3,7,8-Tetrachlorodibenze-P-dioxin (TCDD) or liver carboxykinase and glucose homeostasis and plasma amino acid concentrations in the most TCDD-susceptible and TCDD-resistant rat strains Archtoxicol Aug; 73 (6): 323.

Weber, L. W. D., Grein, H., and Rozman, K. K., (1987): Metabolism and distribution of [14C] glucose in rats treated with TCDD. J. Toxicol. Environ. Health 22, 195-206.

Weber, L. W. D., Ernst, S. W., Stahl, B. U., and rozman, K., (1992): Tissue distribution and Toxicokinetics of 2,3,4,7,8-tetrachlorodibenzo-P-dioxin in distribution and Toxicokinetics of 2,3,4,7,8-tetrachlorodibenzo-P-dioxin in rats after intravenous injection function. Appl. Toxicol. 21, 523-534.

Weber, L. W. D., and Stahl, B. U. (1994): Commentary on the Ah receptor, by A. B. Okey, D. S. Riddick, and P. A-Harper, Toxicol. Lett 70. (1995), pp. 1-22.

WHO (1994): Polybrominated Biphenyls. Environmental Health Criteria 152. World Health Organization, Geneva.

فقدان الوزن كنتيجة لتعرض الفئران البيضاء لمركب 2، 3، 7، 8 - رباعى كلورو ثنائى بنزو-بارا-دايوكسين

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يعد التلوث البيئي من أهم مشكلات عالمنا المعاصر. وتشكل مبيدات الآفات على اختلاف أنواعها واحداً من أهم وأخطر تلك المصادر وذلك لتأثيرها المباشر على مكونات البيئة من هواء وماء وتربة وغذاء . وتكمن خطورة هذه المركبات في خاصيتها التراكمية وزيادة تركيزاتها في التربة وكذا أنسجة وأعضاء الحيوانات والطيور والأسماك المتعرضة لها . وكذلك في أنسجة الإنسان المتعرض لهذه المركبات مما يجعلها مصدراً متجدداً للتلوث ولفترات طويلة. ومع تزايد الاهتمام بدراسة الآثار السلبية المتعددة والمختلفة نتيجة استخدام هذه المركبات فقد تم اختيار مركب الديوكسين لهذه الدراسة . يمتلك هذا المركب خصوصية شديدة لكونه لا يستخدم تجاريا أو صناعيا إلا أنه ينبعث كناتج جانبي أو فرعى عند تصنيع بعض المبيدات العشبية أو عند تعرضها لدرجات حرارة عالية مثل مركب الـ 2,4-D مما يتسبب في انبعاث كميات كبيرة من الديوكسين عند تصنيعه لعدم انضباط درجة الحرارة أو عند تعرضه لدرجات حرارة عالية بعد التصنيع. ولذلك تم اختيار مركب التتراكلورو داى بنزوديوكسين (TCDD) لهذه الدراسة لمعرفة بعض التأثيرات السمية له وتم اختيار فئران التجارب البيضاء كموديل (أو حيوانات تجارب) لإجراء هذه الدراسة وذلك لحساسيتها المتوسطة لهذا المركب.

ولقد تم استخدام عدد 200 فأر أبيض ذكر عمر 10 – 12 أسبوع تراوحت أوزانها عند التجربة بين100-150جرام و تم أقلمتها وتربيتها في أقفاص الفئران الخاصة بهذا الغرض. ويهدف البحث إلى دراسة التأثيرات السامة لمادة الديوكسين على الفئران البيضاء من حيث دراسة أثر الديوكسين على معدل الزيادة في وزن الجسم واستهلاك الغذاء وكذلك على مستوى كل من الكوليسترول والتراى جليسريد بالإضافة إلي مستوى هرمون الثيروكسين وسكر الجلوكوز في مصل الدم . وكذلك دراسة تأثير فيتامين ج كمحاولة للعلاج في حالة التعرض طويل المدى لمادة الديوكسين.

تم تقسيم هذه الفئران إلى خمس مجموعات بكل منها أربعون فارا. تم إعطاء المجموعة الأولى مركب الديوكسين بواقع 4,. ميكروجرام/كيلوجرام من وزن الجسم والمساوي لـ 5/1 الجرعة المتوسطة المميتة لهذا المركب مذابة في زيت الذرة مرة واحدة فقط عن طريق الفم بأنبوب اللي المعدي بينما تركت المجموعة الثانية ضابطة للتجربة الأولى . المجموعة الثالثة تم إعطاءها الديوكسين بواقع 44,. ميكروجرام/كيلوجرام من وزن الجسم والمساوي لـ 50/1 من الجرعة المميتة المتوسطة مذابة في زيت الذرة يوماً بعد يوم ولمدة 12 أسبوع عن طريق الفم بأنبوبة اللي المعدي . أما المجموعة الرابعة فقد عوملت بنفس الجرعة السابقة مع إضافة فيتامين ج لماء الشرب بواقع 1 جم/لتر ماء. بينما تركت المجموعة الخامسة والأخيرة كضابط للمجموعتين الثالثة والرابعة.

قد تم تجميع العينات بعد144,96,72,48,24,12 ساعة بعد التعرض لمركب الديوكسين في المجموعتين الأولى والثانية بينما تم تجميع العينات في المجموعات الثالثة والرابعة والخامسة بعد 4 و6 و8 و10 و12 أسبوع من التعرض, كما تم أيضا متابعة الفئران وأخذ العينات لمدة أسبوعين بعد إيقاف التعرض. وكذلك فقد تم وزن كمية الغذاء المستهلك وأيضا وزن الجسم في المجموعتين الثالثة والرابعة ومقارنتهما بالمجموعة الضابطة طوال فترة التجربة, وتم فصل مصل الدم واستخدامه في قياس تركيز بعض نواتج التمثيل الغذائي (الكوليسترول – الترايجليسريد والجلوكوز) وقياس مستوى هرمون الثيروكسين في الدم .

أظهرت النتائج انخفاض معنوي في كل من معدل الزيادة في وزن الجسم وأيضا في كمية الغذاء المستهلك مقارنة بالمجموعة الضابطة.كما سجلت النتائج نقص في مستوى الجلوكوز والثيروكسين في الدم وكذلك أظهرت النتائج زيادة معنوية في نسبة كل من الكوليسترول والدهون الثلاثية.

وقد استخلص من نتائج هذه الدراسة أن التعرض للديوكسين في كل من التسمم الحاد وطويل المدى يؤدى إلى انخفاض ملحوظ في وزن الجسم وأيضا في كمية الغذاء المستهلك في الفئران المتعرضة, مصحوبا بانخفاض ملحوظ في مستوى كل من الجلوكوز وهرمون الثيروكسين في الجسم ومن هذا يتضح أن التغيرات التي تحدث في التمثيل الغذائي للمركبات الدهنية والكربوهيدراتية هي من أهم النتائج التي تلي التعرض الطويل المدى للديوكسين مؤديا إلى فقد الدهون ونقص في وزن العضلات من الجسم (wasting syndrome) ولم يظهر أي تأثير ملحوظ لفيتامين ج لعلاج هذه التغيرات الناتجة من التعرض لمركب الديوكسين.

ولذلك ينصح باستبدال المركبات المستخدمة كمبيدات أو كمواد حافظة للأخشاب والتي ينبعث من تصنيعها أو استخدامها هذا المركب المعروف باسم الديوكسين بأخرى تكون صديقة للبيئة . كما ينصح بعمل مسح دوري للتربة وللمنتجات الغذائية على اختلاف أنواعها لمركب الديوكسين وخصوصاً المنتجات الغذائية المحتوية على المنتجات الحيوانية كاللحوم والألبان . كما ينصح بتلافى المصادر الأخرى لهذا المركب بمنع حرق المخلفات البلاستيكية والتخلص منها بطريقة علمية صحيحة لكي نمنع مصدراً رئيسياً لتلوث البيئة بهذا المركب الخطير على الصحة العامة للإنسان والحيوان على حد سواء . كما تشير نتائج هذه الدراسة إلى أهمية إعادة البحث بصورة أوسع لبيان تأثير المركبات المضادة للأكسدة عامة وفيتامين ج بصورة خاصة في الوقاية من الآثار السامة لهذا المركب.